form a sound basis for demonstrating analytical similarity. Given below is a stepwise approach to developing a plan for analytical similarity demonstration:

- Evaluate quality attributes consistent with the risk assessment principles ICH Quality Guidelines Q8, Q9, Q10, and Q11.
- Consider criticality risk ranking of quality attributes with regard to their potential impact on activity, PK/PD, safety, and immunogenicity.
- Use a tiered approach for assessment as suggested by the FDA:
  - Equivalence interval testing for *some* high-risk attributes (c*σ_R; c=1.5 unless otherwise justified a higher number) (Tier 1).
  - Quality ranges (mean ± X*SD) for *other* high- to low-risk attributes; generally X=3 or lower (Tier 2).
  - Raw/graphical comparisons for *other* attributes (Tier 3); graphical output may come in the evaluation of high-risk attributes. Tier 3 refers to the presentation of data and does not necessarily mean an irrelevant attribute.

The regulatory agencies require that the biosimilar product developer create a risk-based model to identify the critical attributes, critical to safety, potency, and purity that can make a meaningful difference in *commercial supply* of the product. For identifying CQAs at various stages of the manufacturing process, most biosimilar product developers assign CQAs based on the MOA or PK, which are believed to be relevant to clinical outcomes. It is a reasonable assumption that change in the MOA or PK of a given quality attribute is predictive of clinical outcomes. However, the primary assumption that there is a well-established relationship between in vitro assays and in vivo testing (i.e., in vitro assays and in vivo testing correlation) needs to be validated. Under the validated in vitro assays and in vivo testing correlation relationship, the criticality (or risk ranking) can then be assessed based on the degree of the relationship. In practice, most biosimilar product developers provide clinical rationales for the assignment of the CQAs without using a statistical approach for the establishment of in vitro assays and in vivo testing correlation. The assignment of the CQAs without using a statistical approach is considered subjective and hence is somewhat misleading.

The biosimilar product developers face many challenges including a limited number of lots of reference product available, different testing methods resulting in different data types, and on deciding what difference is meaningful and what is not, finally establishing acceptable similarity margins and presenting the data in a convincing manner. “The plurality of candidates of critical quality attributes within specific developments, as well as the usually low number of drug lots available, had been identified as the most limiting factors, rendering the use of statistical routines usually performed on the basis of patient clinical data inappropriate most of the time” (EMA 2013).